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Role for catecholamines in tumor progression

Possible use for β-blockers in the treatment of cancer

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Commentary to: Dong Zhang, Qing Yong Ma, Heng-Tong Hu and Min Zhang. β2-adrenergic antagonists suppress pancreatic cancer cell invasion by inhibiting CREB, NFκB and AP-1. Cancer Biol Ther 2010; This issue.

Interest in the efficacy of β-blocking agents as possible additions to cancer treatment paradigms has been gaining momentum in recent years. In this issue of *Cancer Biology & Therapy*, Zhang et al. report that β-adrenergic receptors (ARs) may play a role in pancreatic cancer invasion, and support the idea that β-blockers may be useful in suppressing pancreatic cancer invasion and proliferation.[1] This study adds to the growing literature that describe the impact of catecholamines, including norepinephrine (NE) and epinephrine (EPI), on tumor progression. In this study, they show that MIA PaCa-2 and BxPC-3 pancreatic cancer cell lines express mRNA and protein for both β1- and β2-ARs. When treated with the β2-AR-specific antagonist, ICI118,551, and the non-specific β-AR antagonist, propranolol, cell invasion and proliferation were significantly inhibited in a Matrigel invasion and subrenal capsular assays. This effect was greater compared to the β1-AR antagonist, metoprolol and control. The β2-AR-mediated effect on invasion and proliferation was shown to be through the modulation of vascular endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-2, MMP-9 and cyclooxygenase (COX)-2, and involves the MAPK pathway. This study further adds to the growing number of cancers wherein β-blockers may be included in preventive and therapeutic strategies.

Studies have suggested roles for catecholamines, NE and EPI, in tumor progression by directly affecting tumor cell behavior and gene expression.[2] First, catecholamines have been shown to have a growth promoting effect on tumor cells. For example, EPI has been shown to modulate the growth of tumors induced by a tobacco-specific nitrosamine in the lungs of hamsters suggesting that the interaction of nitrosamine with β-ARs contributes to the progression of this type of lung cancer.[3] Furthermore, studies have shown the possible chemotactic activity of NE-producing organs to recruit tumor cells. For example, the adrenal gland and the brain, two catecholamine-rich organs, are common sites of metastases for several types of malignancies.[4-6] In addition, these stress hormones have been shown to stimulate the migration of, and are potent chemotactic agents for, breast carcinoma cells and colon cancer cells.[7,8] The ability of NE to increase the metastases of PC-3 prostate cancer cells to lumbar lymph nodes was further shown in athymic BALB/c nude mice; this effect was inhibited by propranolol.[9] In addition, catecholamines have been shown to have an anti-apoptotic effect on cancer cells and may render tumor cells resistant to chemotherapeutic drugs. Specifically, physiological levels of EPI have been shown to protect LNCaP and C4-2 prostate cancer and MDA-MB-231 breast cancer cells from apoptosis, an effect that is mediated by the β2-AR and PKA-dependent phosphorylation of BAD (BCL2-antagonist of cell death) protein.[10] Finally, treatment of MDA-MB-231 cells with NE or EPI (or cortisol) in vitro has been shown to reverse the G_2/M cell cycle arrest and cytotoxicity induced by the chemotherapeutic drug paclitaxel (Taxol).[11]

Studies in the field of psychoneuroimmunology have described the complex bi-directional interactions among the central nervous system, the endocrine system and the immune system and have implicated behavior/psychological stress as a factor that can influence several aspects of health, including cancer. Initially, the impact of stress on cancer has been shown to be through the modulation of the immune response with cytokines mediating the bi-directional communication among the nervous, endocrine and immune systems that form a complex network. This Involves the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal medullary axis (SAM) and leads to the production of biological mediators including the catecholamine stress hormones, NE and EPI. A number of recent studies in this field that suggest that stress can also have effects that may contribute to tumor progression independent of its effects on the immune system.[12-16] Work by our group and those of others have since shown that various types of tumor cells express β-ARs and that expression of several pro-angiogenic and prometastatic factors are modulated by catecholamines. For example, studies by Sood, Lutgendorf and colleagues have shown that NE and EPI may influence the progression of ovarian cancer by modulating the expression of MMPs and VEGF in SKOV3, EG and 222 ovarian cancer cells thus stimulating the invasiveness in vitro.[12,14,15] The role of β-ARs in this process was supported by the observation in a mouse model showing that propranolol blocked the significant increase in angiogenesis, tumor volume and infiltration of SKOV3ip1 tumor cells when immunodeficient mice were exposed to restraint stress or treated with the β-AR agonist, isoproterenol. This effect was shown to involve the tumor cell cAMP-PKA signaling pathway.[12,17]

Our group has further shown that NE can promote tumor progression by stimulating the secretion of VEGF, MMP-2, MMP-9, interleukin (IL)-6 and IL-8 and thus enhancing the invasive and pro-angiogenic properties of other tumors including nasopharyngeal carcinoma, multiple myeloma and cutaneous melanoma. The clinical relevance of these studies is supported by the data showing that cells in biopsies of nasopharyngeal carcinoma, multiple myeloma and melanoma tumors express the β2-AR.[13,16,18] These observations support the hypothesis that stress-associated activation of the SAM axis can, in part, promote tumor progression by modulating the expression of pro-angiogenic and pro-metastatic factors.

Although the growing number of studies using cells in culture and in mouse models support the possible utility of β-blockers for cancer therapy, studies examining the association between the use of β-blockers and cancer risk in humans have yielded contradicting results, suggesting the complexity of this relationship. However, several studies point to the association between the use of β-blockers and decrease in cancer risk. For example, Perron et al. showed in an eight year observation of males diagnosed with prostate cancer (2,221 individuals taking antihypertensive drugs and 11,105 well-matched controls) that β-blocker use may prevent the disease. Their study showed that, of the different classes of antihypertensive drugs, only β-blockers were associated with a reduction in prostate cancer risk.[19] Another study by Algazi and co-workers addressed this issue in a group of 839 patients diagnosed with cardiovascular disease (composed of 326 β-blocker users and 513 subjects on other medications). These subjects were followed up prospectively for an average of 10 years, comparing the risk of cancer in subjects who were using β-blockers and those who were not. After adjusting for sex and age, the researchers observed that 15 cancer cases occurred among β-blocker users while 59 cases occurred in patients who had never used β-blockers in the follow-up period suggesting that β-blocker treatments significantly decreased the risk of cancer.[20]

The paper by Zhang et al. further adds to observations that β-ARs are expressed in several different types of tumors. Studies have shown that β-blockers can abrogate the catecholamine-dependent stimulation of several processes in tumor progression including proliferation, invasion and angiogenesis. As these studies continue to provide data increasing the promise of β-blockers for use in cancer therapy, new questions arise: Do all tumor types express β-ARs? Since stromal cells (including immune cells) in the tumor microevironment have been shown to have significant roles in tumor progression, what effect will β-blockers have on the development of tumors whose cells express no or low levels of β-ARs? While β-blockers are already commonly used clinically for the treatment of various cardiovascular diseases, it is not yet clear whether they can be useful for treating cancers. The studies discussed here contribute to the elucidation of the mechanisms involved in tumor progression and further point to the utilization of β-blockers (in combination with other treatment paradigms) as promising strategies for slowing-down the progression of most malignant disease and improving cancer patients' quality of life.

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